REMARKS

I. Status of the Claims

Claims 26-50 are pending in the application, claims 1-25 having been canceled in a preliminary amendment. In response to the restriction requirement, applicants elected, without traverse, to prosecute claims 26-29, *i.e.*, the Group I claims. Additionally, applicants elected antigen binding for CD19 (claim 28) and the corresponding polypeptide of SEQ ID NO: 1 (claim 29). Thus, claims 26-29 are under examination and claims 30-50 stand withdrawn.

Claim 29 stands rejected under 35 U.S.C. §112, first paragraph, and claims 26-29 stand rejected under 35 U.S.C. §102 over Dorken *et al.* The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, First Paragraph

Claim 29 is rejected as allegedly lacking an adequate written description for sequences 70% homologous to SEQ ID NO. 1 which retain the function of binding to CD19. Applicants traverse.

The first paragraph of 35 U.S.C. §112, requires that the "specification shall contain a written description of the invention ...." This requirement is separate and distinct from the enablement requirement. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). The written description requirement has several policy objectives. "[T]he 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). Another objective is to put the public in possession of what the applicant claims as the invention. See *Regents of the*

University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). "The 'written description' requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed."" *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. However, a showing of possession alone does not cure the lack of a written description. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 969-70, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002). There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) ("we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims").

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by

showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, *e.g.*, *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)

Claim 29 was an original claim. Thus, the burden on the examiner to show lack of written description is high. Moreover, the present specification describes six different bispecific constructs set forth as SEQ ID NOS: 1-6, each of which binds to CD3 and CD19, including the corresponding VH and VL chains and the corresponding CDRs (see page 11 of the corresponding WO 2005/052004). On page 12, first paragraph of the WO 2005/052004, the specification discloses methods for carrying out sequence alignments which can be used to identify bispecific constructs which are at least 70% homologous to the CD3 and CD19 binding construct depicted in SEQ ID NO: 1:

> Within this embodiment, the term "substantially equivalent to" is understood to comprise amino acid sequences homologous to any of SEQ ID NOs: 1-6 by at least 70%, based on a comparison of primary amino acid sequence. Such degrees of homology may be determined by standard sequence alignment programs such as Vector NTI (InforMax™, Maryland, USA). Such programs compare aligned sequences on an amino acid-by-amino acid basis, and can be set to various levels of stringency for the comparison (e.g. identical amino acid, conservative amino acid substitution, etc.). Within the meaning of this embodiment, two amino acids in question are considered as being "homologous" when they are either identical to one another or conservative substitutions of one another. By way of non-limiting example, two different amino acids belonging to the class of lipophilic amino acids would be considered homologous in the sense of this embodiment, even if these two amino acids were not identical, whereas a lipophilic amino acid on the one hand and a charged acidic amino acid on the other hand would not be considered homologous.

Thus, there is little question that applicants clearly contemplated the use of sequences other than those specified, including those with homologies of at least 70%. It also provided information showing possession these embodiment, thereby addressing the written description requirement.

Reconsideration and withdrawal of the rejection is therefore respectfully requested.

III. Rejection Under 35 U.S.C. §102

Claims 26-29 are rejected as anticipated by Dorken *et al.*, U.S. Patent 7,112,324. The examiner apparently takes the view that the isolation of a monomeric fraction depicted in, *e.g.*, Figures 10 and 11 of Dorken (analysis of the purified bscCD19xCD3 bispecific antibody) anticipates the subject matter of the present claims. Applicants traverse.

A careful reading of the description of Example 6 of Dorken provides that purity of the column fractions has been examined under denaturing conditions. "Purity of column fractions was assessed by ***reducing*** sodium dodecyl sulfate (SDS Bis/Tris 4-12 % polyacrylamide gradient gel electrophoresis (PAGE) employing a MOPS buffer system (Novex)" (emphasis added; page 25, line 51-54). However, following the teachings of Example 6 of Dorken, multimeric and monomeric bispecific antibody constructs cannot be distinguished, because the multimeric proteins would have all been dissociated into monomeric proteins. Thus, importantly, the purification methods described in Dorken do not generate a composition comprising the monomer:multimer ratio as now recited in claim 26, *i.e.*, a ratio where the multimeric form of the polypeptide constitutes no more than 5% of the total weight of the combined monomeric + multimeric forms of said polypeptide.

As shown in Example 3 of the present application, a number of bispecific antibodies were produced in Chinese hamster ovary (CHO) cells according to generally known procedures

(Sambrook *et al.*, 1989). Each bispecific single chain antibody produced contains two antigen binding sites, each antigen binding site containing one VH and one VL region. One of the two antigen binding sites in each molecule is specific for the human CD3 antigen. The other antigen binding site (target antigen binding site) is specific for a desired target antigen other than the human CD3 antigen, including *inter alia* CD19. Construct 1 in Table 1 of the present application corresponds to the bispecific construct binding to CD3 and CD19 shown in SEQ ID NO. 1. Ratios of the polypeptide in monomeric/multimeric (here, dimeric) form were determined by a combination of SDS-PAGE performed under reducing conditions, Western Blot performed using Penta-His (Qiagen) and Goat-anti-mouse-AP (Sigma) antibodies and gel filtration performed on a Sephadex S200 column.

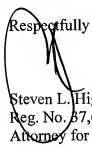
The relative proportions of bispecific single chain polypeptide present in dimeric form are shown in Table 1 for polypeptides comprising target antigen specificities against the human CD19 antigen (*i.e.*, the CD3 and CD19 binding construct shown in SEQ ID NO. 1), the human EpCAM antigen, the human Wue1 antigen (a highly specific multiple myeloma antigen) and the human sTn antigen (a carbohydrate displayed on the epithelium of malignant cells in breast, prostate and colon cancers). As can clearly be seen in Table 1, each bispecific single chain antibody with anti-human CD3 antigen binding specificity, including SEQ ID NO. 1, spontaneously forms significant amounts of multimeric (*i.e.*, here, dimeric) species when left uncontrolled. The propensity to spontaneously form homodimers therefore appears to be a generic characteristic of the class of the bispecific single chain antibodies examined. Thus, even if one were to look at Dorken's composition using the purification methods described by Dorken, it would not meet the recitation of less than 5% multimeric protein.

In light of the foregoing information, it is clear that the procedures described in the cited art do not allow the skilled artisan to separate monomeric and multimeric forms of the bispecific antibody constructs so as to obtain a mixture with the ratio now specified in claim 26. This subject matter is the product directly obtained by the inventive processes of the present invention. It is only through these processes that the skilled artisan is able to separate the monomeric and multimeric form of the bispecific antibody constructs and to obtain the mixture with the claimed ratio. Consequently, claim 26 as presented for reconsideration is not anticipated by Dorken. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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